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Neuroprotective strategies in cardiac surgery: a survey among South African anaesthesiologists

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NEUROPROTECTIVE STRATEGIES IN CARDIAC SURGERY: A SURVEY AMONG SOUTH AFRICAN ANAESTHESIOLOGISTS

Nthabiseng Jacqueline Kumalo

A research report submitted to the Faculty of Health Science,

University of the Witwatersrand, Johannesburg,

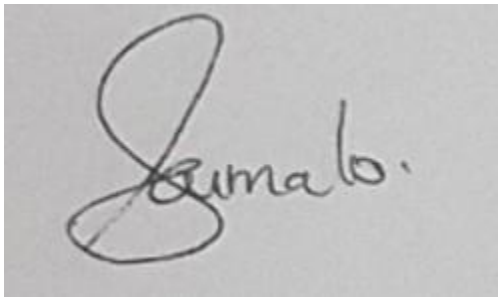
in the partial fulfilment of the requirements for the degree of

Master of Medicine in the branch of Anaesthesiology

Johannesburg, 2023

Declaration

I, Nthabiseng Jacqueline Kumalo, herewith declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



_____

Signed

On this_29__day of September 2023.

Dedication

To Sir Jose Bright, thank you for everything Dad. I am because you are, may you continue to rest in peace.

Presentations and publications from this research project

1. No presentation from this research project
2. No review article submitted on this research project.

Abstract

Background

The occurrence of neurological injury and cognitive disorders post cardiac surgery is a known complication that is described in literature. Neuroprotective strategies utilised intraoperatively can significantly improve postoperative neurological outcomes. The current challenge is the lack of standardised practice and protocols for intraoperative neuroprotection during cardiac surgery. This study looks at some of the currently applied neuroprotection strategies by clinicians during cardiac surgery.

Methods

A cross sectional,descriptive, contextual study was conducted amongst cardiothoracic anaesthetists and registrars in South Africa. A google link survey of the questionnaire consisting of 15 questions and 2 comment sections was sent out. To adhere to the protection of personal information act (POPIA), the questionnaire was centrally distributed via administration by the Cardiac Anaesthesia Society of South Africa (CASSA) and the South African Society of Anaesthesia (SASA), to its members. A link was shared with the members of CASSA during the Joint Peri-Operative Cardiothoracic (JPC) Annual Congress on the 20th of November 2021, and with the SASA members on the weekly online communication platform for the month of February 2022.

Results

A total of 101 clinicians around South Africa, involved in administering anaesthesia to patients requiring cardiac surgery, participated in this questionnaire. There is lack of

standardized care for neuroprotection during cardiac surgery and availability on the stroke rates in most institutions. TTE use was preferred for atheromatous plaque assessment with epiaortic scanning barely used.

Conclusion

There is lack of standardised guidelines for the anaesthetic management of this high-risk population in academic and private centres across South Africa. This finding exposes a niche to be further explored by researchers to come up with preventative or risk minimising protocols during conduction of anaesthesia during the cardiopulmonary bypass (CPB) period.

Acknowledgements

I would like to extend my gratitude to my supervisors for their continued support with my research and their academic guidance in ensuring success of this research project. I would also like to acknowledge my statistician for his great help with the statistical component of this research project.

I am grateful to God for seeing me through this journey and carrying me through right to the end. To my family, thank you.

TABLE OF CONTENT

DECLARATION II

DEDICATION III

PRESENTATION AND PUBLICATION FROM THIS RESEARCH PROJECT IV

ABTSRACT V

Background v

Methods v

Results iv

Conclusion vi

ACKNOWLEGEMENTS VII

LIST OF FIGURES X

LIST OF TABLES XI

APPENDICES LIST XII

LIST OF ABBREVIATIONS XIII-XIV

ARTICLE 1

Introduction 2

Methods 3

Results 6

Discussion 9

Limitations 17

Conclusion 18

Reference 19`

APPENDICES 25

LIST OF FIGURES

Figure 1: Method flow diagram 5

Figure 2: TEE use during cardiac surgery on CPB to assess the aortic atheromatous burden 7

Figure 3:Epi-aortic ultrasound use among anaesthetists 8

Figure 4: The presence of institutional guidelines in the BP management during cardiac surgery on CPB 8

Figure 5: The choice of pharmacological agents used for intraoperative neuroprotection 10

LIST OF TABLES

Table 1: Demographic characteristics of the participants 6

Table 2: Intraoperative neuroprotection mechanisms 9

APPENDICES

Appendix 1: Proposal

Appendix 2: Human research ethics committee clearance certificate

Appendix 3: Turn it in report.

Appendix 4: Journal Guidelines to authors

Appendix 5: Charlotte Maxeke Johannesburg Academic Hospital CEO Approval

Permission letter by CASSA president

Appendix 6 Permission letter by Charlotte Maxeke Johannesburg Academic hospital HOD anaesthesia

Appendix 7: Permission letter by CASSA president

Appendix 8: Permission letter by SASSA CEO

Appendix 9: National Heath Research Database Approval

Appendix 10: Data collection sheet

LIST OF ABBREVIATIONS

POCD: postoperative cognitive dysfunction

CVA: cardiovascular accident

CABG: coronary artery bypass graft

CPB: cardiopulmonary bypass

TEE: transoesophageal echocardiogram

NIRS: near-infrared spectrometry

CASSA: Cardiothoracic Anaesthesia Society of South Africa

SASA: South African Society of Anaesthesiologists

Cardiothoracic Anaesthesia Society of South Africa (CASSA)

Cardiopulmonary Bypass (CPB)

Trans Oesophageal Echocardiography (TEE)

Near Infrared Spectrometry (NIRS)

Coronary Artery Bypass Graft (CABG

Draft Article

Neuroprotective strategies in cardiac surgery: a survey among South African Anaesthesiologists

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Introduction

Adverse neurological outcomes post cardiac surgery result in increased morbidity and mortality. The incidence of strokes following cardiac surgery is reported to be 2 to 4%, and it is much higher in patients with a previous history of strokes, [1]while postoperative cognitive dysfunction (POCD) is as high as 53% at hospital discharge. [2]The aetiology is multifactorial which includes cerebral hypoperfusion, anaemia, high oxygen consumption and perioperative embolic events originating most commonly from the thoracic aorta. [3]

There is a correlation between aortic atheromatous disease and increased risk of developing strokes perioperatively in cardiac surgery as a result of cerebral microembolization. [4]Cerebral microembolization from aortic atherosclerotic lesions and the cardiopulmonary bypass (CPB) circuit during CPB may lead to cognitive decline after cardiac surgery, [5]which makes the assessment of the atheromatous disease important.

Cerebral autoregulation is the ability of the brain vasculature to maintain cerebral blood flow despite changes in blood pressure.[6] Cerebral autoregulation occurs if cerebral perfusion pressure is within normal physiological range. The target optimal blood pressure during CPB has not yet been defined and its usually maintained at 60mmHg which is arbitrary. [1] Devices such as cerebral oximetry may be used to maintain cerebral oxygen saturation within a certain range, based on measurements taken preinduction of anaesthesia. [7]Near Infrared Spectrometry (NIRS) can be used to clinically monitor cerebral blood flow. Real time monitoring of autoregulation with cerebral oximetry may provide a more rational way of individualizing Mean Arterial Pressure (MAP) to maintain cerebral perfusion during CPB. [7]

Evidence to support pharmacological neuroprotection is not robust as most of the suggested strategies are based on animal studies.[8] The modern concept of neuroprotection is receptor mediated protective action by targeting certain receptors such as GABA resulting in inhibition of calcium influx, which in turn protects the brain from evolving or ongoing damage after the initial insult meaning neuroprotection focuses in reducing insult severity [7] Despite impressive short-term protection, studies have failed to demonstrate long term protection by anaesthetic agents.[7] The aim of this study is to ascertain current neuroprotective strategies employed by South African anaesthetists and registrars during cardiac surgery, with the aim of assessing use of commonly employed strategies focusing on assessment of aortic plaque burden, management of intraoperative blood pressures, use of cerebral oximetry, pharmacological methods and compared practice amongst clinicians.

Methods

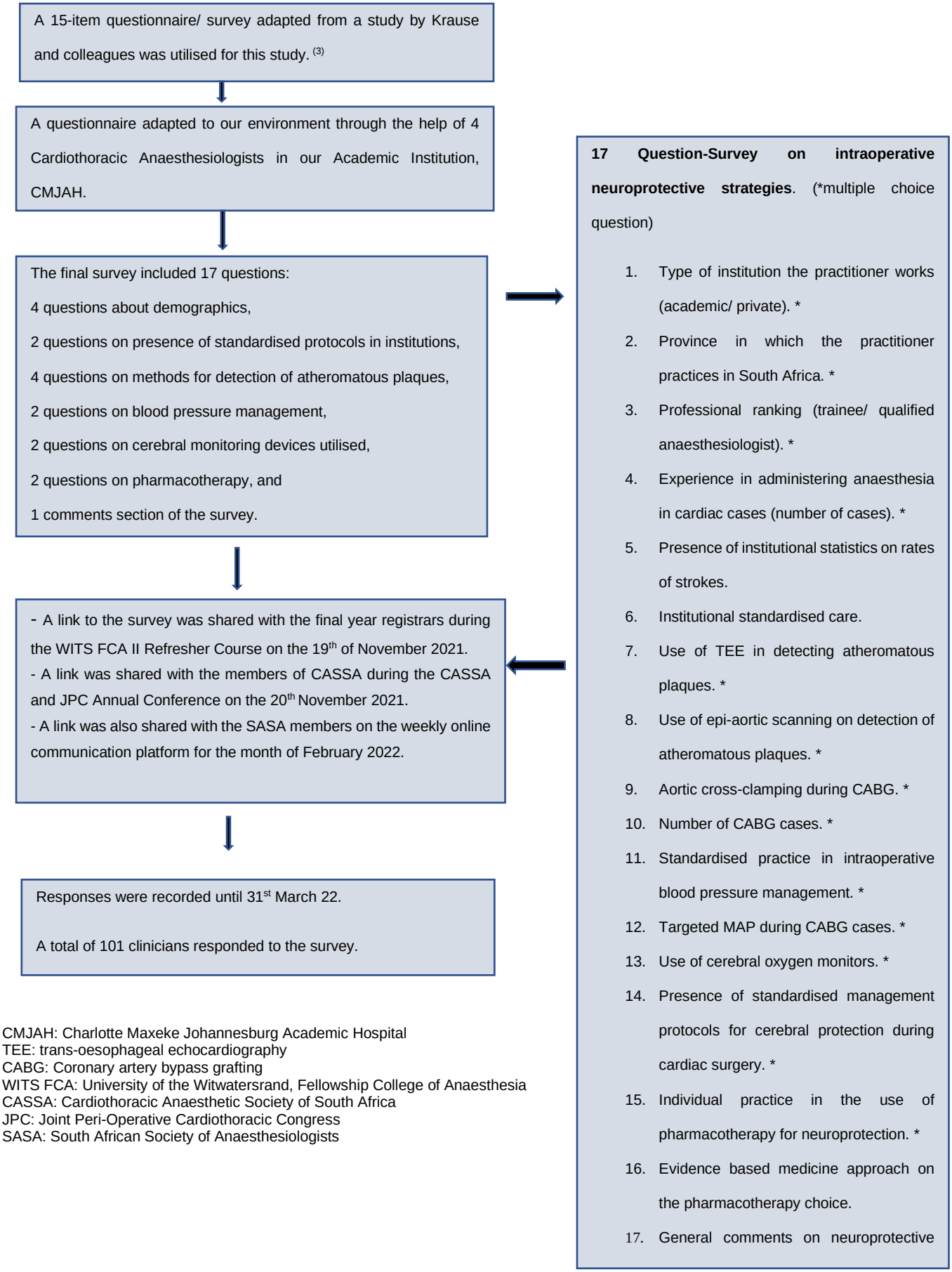
The sample size was calculated using the total number of cardiothoracic anaesthesia society of South Africa (CASSA) members and South African Society of Anaesthesiologist (SASA) members. CASSA has 75 registered members and SASA 2500 including the 75 CASSA members, registrars were 421 across the country and about 70 had completed their cardiothoracic anaesthesia senior rotation at the time of the study. A minimum sample size of 140 was calculated with a 95% confidence interval and 5% margin of error using the Raosoft sample size calculator.

Approval to conduct the study was obtained from the president of (CASSA), Chief Executive Officer (CEO) of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Head of Department (HOD) of Anaesthesia and (SASA). Ethics approval

was granted by the Wits Human Research Ethics Counsel (HREC), clearance certificate no.M211068 and the study was registered with National Health Research Database (NHRD). Consent was implied by completion of a questionnaire as stated in the information sheet. The questionnaire was adopted from a study by Krause et al [3]after an email was sent requesting permission from the author to modify and utilize it in our population of cardiac specialists. The questionnaire was reviewed by four senior cardiac specialists in our department and modified for our clinical settings.

A google link survey of the questionnaire (Appendix 8) consisting of 15 questions and 2 comment sections was sent out. To adhere to the protection of personal information act (POPIA) the questionnaire was centrally distributed via administration by CASSA and SASA to its members. The preceding question had to be answered to be able to move to the next one, participants could select more than one option per question and answers could be changed at any point prior to submission. To reach a greater participant number, the questionnaire was also published on the SASA weekly newsletter for a month. For this study an anaesthetist is a qualified practitioner who provides anaesthesia to cardiac patients regularly (at least 1 to 2 cases per week), either in state or private sector and registrar is an anaesthetist in training to becoming a specialist anaesthetist, that is or has rotated in the cardiothoracic rotation at an academic hospital.

FIGURE 1: METHOD FLOW DIAGRAM



CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
TEE: trans-oesophageal echocardiography
CABG: Coronary artery bypass grafting
WITS FCA: University of the Witwatersrand, Fellowship College of Anaesthesia
CASSA: Cardiothoracic Anaesthetic Society of South Africa
JPC: Joint Peri-Operative Cardiothoracic Congress
SASA: South African Society of Anaesthesiologists

Results

A total of 101 participants (anaesthesiologists, registrars and other) in South Africa, involved in perioperative cardiac surgery, participated in this questionnaire (Table 1).

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF THE PARTICIPANTS

Characteristics (# of responses) N= 101	N (%)
I work…	
…at an academic institution	82 (81.2)
…in private	9 (9.9)
…academic and private	8 (7.9)
…other	2 (2.2)
I practice in the following province…	
…Gauteng Province	54 (53.5)
…KwaZulu Natal	11 (10.9)
…Western Cape	23 (22.8)
…Eastern Cape	7 (6.9)
…Northern Cape	1 (1.0)
…Limpopo	0 (0.0)
…Mpumalanga	0 (0.0)
…North West	0 (0.0)
…Free State	5 (4.9)
My role is…	
…Anaesthesiologist	34 (33.7)
…Registrar	62 (61.4)
…other	5 (4.9)
In my practice, I have performed... number of open-heart procedures…	
< 200	78 (77.2)
201 – 500	8 (7.9)
501 – 1000	3 (3.0)
> 1000	7 (6.9)
I don't know	5 (4.9)
Availability of institutional statistics on rates of strokes/ cerebral injury…	
…yes	25 (24.7)
…no	76 (75.2)
Organised efforts to standardise care to reduce incidence of strokes and cerebral injury post cardiac surgery.	
…Yes	41 (40.6)
…No	26 (25.7)
…Don't know	34 (33.7)

Most of them came from Gauteng province (53.5%) (Table 1). Most participants (82/101) worked in academic institutions. Although the survey reported promising efforts (41%) by institutions to standardise care to improve on patient outcomes, there

seemed to be no institutional statistics on rates of strokes/cerebral injury following cardiac surgery on CPB (75 %).

The use of TEE intraoperatively was favoured by both registrars and anaesthesiologists equally (Figure 2). However, compared to anaesthesiologists, a significant proportion of registrars believed the use of TEE was either guided by guidelines or did not know. Registrars did not know about use of epi-aortic ultrasound in assessing the aortic atheromatous burden (Figure 3). Majority of anaesthesiologists, whilst they knew about it, did not seem to use epi-aortic ultrasound.

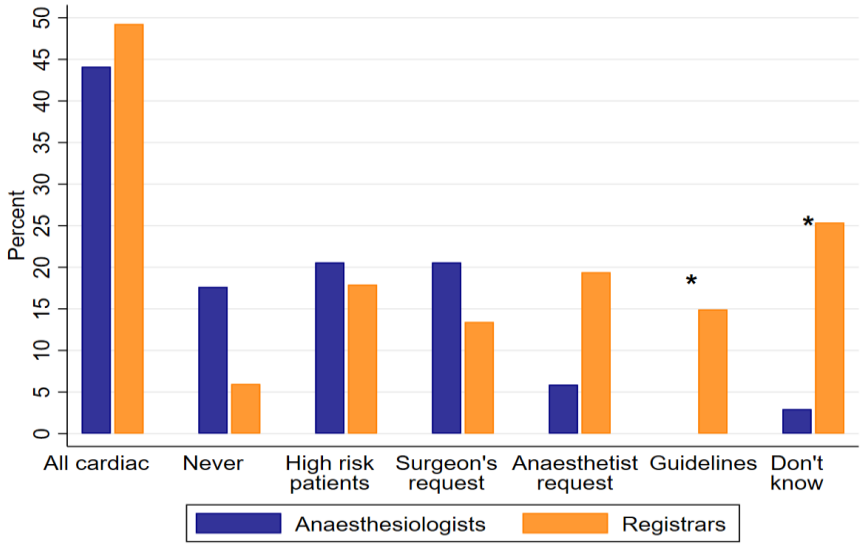


FIGURE 2: TEE USE DURING CARDIAC SURGERY ON CPB TO ASSESS THE AORTIC ATHEROMATOUS BURDEN

TEE (transoesophageal echocardiography); CPB (cardiopulmonary bypass)

* P<0.05

There was a general expression of a lack of established standardised guidelines in use with regards to the management of MAP during cardiac surgery on CPB (Figure 4). Despite the absence of established guidelines, a significant proportion of participants advocated for MAP above 65 mmHg (35.6%), while registrars favoured goal-directed perfusion when compared to cardiac anaesthesiologists (Table 2).

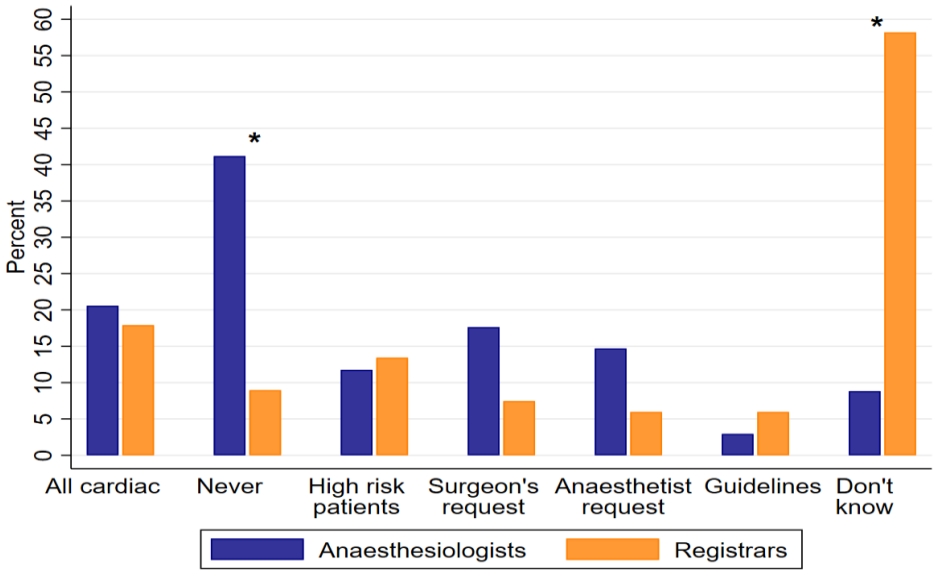


FIGURE 3:EPI-AORTIC ULTRASOUND USE AMONG ANAESTHETISTS

*P<0.05

Majority of both registrars (67.2%) and anaesthesiologists (41.2%) did not know about performance of aortic double clamping during CABG, with significant differences in this knowledge between the two groups (Table 2). Off-pump CABG was not routinely practiced in most South African cardiac centres.

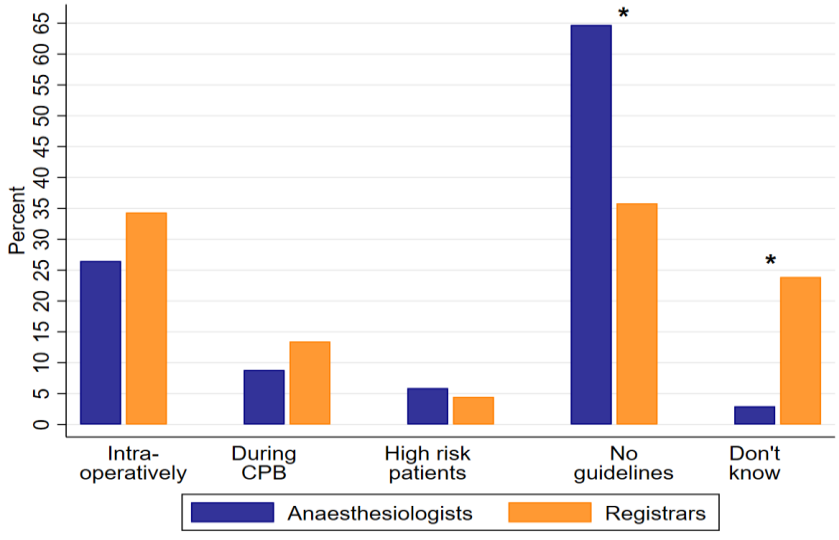


FIGURE 4: THE PRESENCE OF INSTITUTIONAL GUIDELINES IN THE BP MANAGEMENT DURING CARDIAC SURGERY ON CPB

BP (blood pressure), CPB (cardiopulmonary bypass) *P <0.05

TABLE 2: INTRAOPERATIVE NEUROPROTECTION MECHANISMS

Variable	Category	Total N= 101 n (%)	Anaesthesiologist. N = 34 n (33.7%)	Registrar. N =67 n (66.3%)	p-value
Performance of aorta double clamping during CABG	81 – 100	14 (13.9)	4 (11.8)	10 (14.9)	0.004
	61 – 80	6 (5.9)	2 (5.9)	4 (6.0)	
	41 – 60	3 (3.0)	1 (2.9)	2 (3.0)	
	21 – 40	3 (3.0)	1 (2.9)	2 (3.0)	
	0 – 20	5 (4.9)	2 (5.9)	3 (4.5)	
	Never	11 (10.9)	10 (29.4)	1 (1.5)	
	Don't know	59 (58.4)	14 (41.2)	45 (67.2)	
Percentage off pump CABG	80 – 100	3 (3.0)	0 (0.0)	3 (4.5)	0.11
	61 – 80	1 (1.0)	0 (0.0)	1 (1.5)	
	41 – 60	2 (2.0)	0 (0.0)	2 (3.0)	
	21 – 40	4 (4.0)	2 (5.9)	2 (3.0)	
	0 – 20	56 (55.4)	25 (73.5)	31 (46.3)	
	Never	18 (17.8)	5 (14.7)	13 (19.4)	
	Don't know	17 (16.8)	2 (5.9)	15 (22.4)	
Use of cerebral oxygen saturation monitoring e.g., NIRS to guide therapy	All cardiac	71 (70.3)	24 (70.6)	47 (70.1)	0.96
	Never	9 (8.9)	4 (11.8)	5 (7.5)	0.47
	Increased risk	22 (21.8)	6 (17.6)	16 (23.9)	0.47
	Surgeon's request	2 (2.0)	0 (0.0)	2 (3.0)	0.31
	Anaesthetist request	9 (8.9)	2 (5.9)	7 (10.4)	0.48
	Guidelines/standard procedures	6 (5.9)	1 (2.9)	5 (7.5)	0.66
	Don't know	2 (2.0)	0 (0.0)	2 (3.0)	0.55
MAP targets during CPB in patients at risk for post operative cerebral injury	>45 mmHg	4 (4.0)	1 (2.9)	3 (4.5)	0.50
	>55 mmHg	9 (8.9)	4 (11.8)	5 (7.5)	
	>65 mmHg	36 (35.6)	14 (41.2)	22 (32.8)	
	>75 mmHg	4 (4.0)	2 (5.9)	2 (3.0)	
	>85 mmHg	1 (1.0)	1 (2.9)	0 (0.0)	
	Goal-directed perfusion	18 (17.8)	6 (17.6)	12 (17.9)	
	No target MAP	12 (11.9)	4 (11.8)	8 (11.9)	
	Other	5 (4.9)	1 (2.9)	4 (6.0)	
	Don't know	12 (11.9)	1 (2.9)	11 (16.4)	

Cerebral oximetry monitoring seemed to be a more familiar technique that was utilised by most study participants in all cardiac surgery cases. The choice of pharmacotherapeutic agents use for neuroprotection was significantly different between registrars and anaesthesiologists, with anaesthesiologists advocating for corticosteroids and dexmedetomidine, whilst registrars believed use of opioids was neuroprotective (Figure 5).

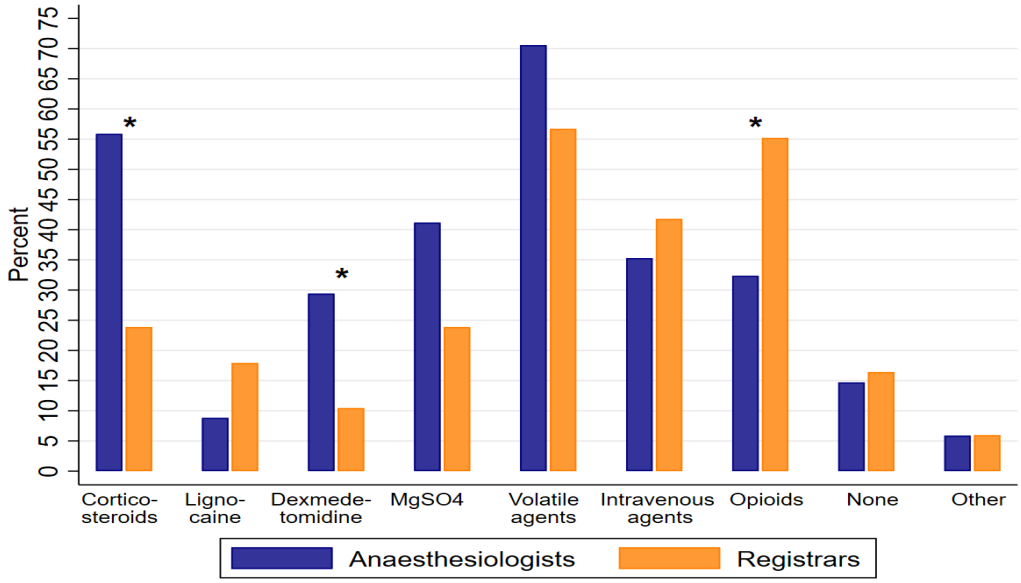


FIGURE 5: THE CHOICE OF PHARMACOLOGICAL AGENTS USED FOR INTRAOPERATIVE NEUROPROTECTION

*P <0.05

Discussion

Our results showed that although it is known that cardiac surgery is associated with neurological injury, there is still lack of information in most institutions relating to the gravity of this complication, with only a quarter of the participants having access to this information. Efforts to standardize care to reduce the rates of strokes and cerebral injury is promising but still low.

The use of TEE was favoured amongst anaesthesiologist and registrar equally, although the registrars thought that TEE use was based on guidelines and did not know that it was used to assess atheromatous burden. TEE can be used to assess for air emboli post closure of cardiac chambers, particularly left sided chambers, to avoid air emboli migrating to the brain. [9] It can also be used to assess thromboembolic load which may be related to coagulation defects and or inadvertent anticoagulation mismanagement intraoperatively. [10] Both TEE and intraoperative epi-aortic

ultrasound scanning allow for aorta visualisation, quantification of aortic atheroma according to thickness and presence of mobile components. [11] This is important for avoiding cannulation through the plague causing emboli to dislodge. [11] In the literature epi -aortic scanning is demonstrated to be superior than TEE and palpation.[12] This was demonstrated in a study assessing digital palpation (DP), transoesophageal echocardiography (TEE) and epi-aortic scanning (EAS) in 154 subjects undergoing elective cardiac surgery, looking at the presence or absence of the atheroma. [12] Digital palpation was the least sensitive at 12%, followed by TEE at 53% and EAS at 81%. This study supported that detection of atheroma should be performed with EAS. [12]Davila et al. also demonstrated the effectiveness of intraoperative epi-aortic ultrasound versus TEE in assessing aortic atherosclerosis during cardiac surgery in a prospective study of 44 patients. [13]In their study atherosclerosis was graded by severity as normal, mild, moderate, and severe. The epi-aortic ultrasound was more accurate at detection and grading of severity. [13] In the current study, registrars did not know about epi-aortic ultrasound and the anaesthesiologist, although knowledgeable about it, did not apply it in their practice.

In our study both groups reported the absence of guidelines for blood pressure management during cardiac surgery on CPB, while both advocated for MAP target of above 65 mmHg, registrars also favoured goal directed perfusion compared to anaesthesiologists. Mean arterial pressure (MAP) management during cardiac surgery on cardiopulmonary bypass (CPB) is thought to be one of the contributing factors to neurological injury, and the target optimal blood pressure has not yet been established. [1] Equivocal views exist about optimal MAP during CPB. A retrospective study involving 1000 patients who underwent coronary artery graft looked at the

influence of cerebral perfusion pressure (CPP) [14] and MAP dispersion on neurological outcomes. Their results showed that it was not only age, duration on CPB and a history of previous strokes that were contributing as risk factors, but that a high MAP fluctuation had the highest incidence of stroke development in these patients. [14] Another study by Vedel et al showed no difference in prevention of cerebral injury between the high or low mean arterial pressures targets during cardiac surgery on cardiopulmonary bypass, MAP was maintained at (70-80mmHg) in high group versus (40-80mmHg) in the low group [15] A total of 193 patients were enrolled, and randomly split. The outcome looked at was new cerebral ischaemic lesions. Results showed that low or high mean arterial targets during CPB did not affect the size or volume of new cerebral infarct. [15]

Majority of both the registrars and anaesthesiologist did not know anything about double aortic clamping during CABG with a significant knowledge difference in both groups. Performance of off-pump CABG was not routinely performed is South Africa with less than 20% of cases having been done by both registrars and anaesthesiologists in this survey. Aortic cross clamping during cardiac surgery interrupts blood flow through the aorta allowing for surgical repair. [16] Ates et al conducted a retrospective study assessing cardiac and neurological complications peri and post operatively with single versus double aortic clamping technique. The was no significant difference in outcome between the two techniques. [17] Another study investigated whether elimination of cross aortic clamping during coronary artery bypass grafting (CABG) reduced strokes postoperatively. [18] In this study the use of aortic cross clamping resulted in higher rates of strokes. [18]

There is a debate regarding neuroprotective advantages of off-pump versus on-pump coronary artery bypass graft (CABG). The Octopus study in 2007 investigated the long-term cognitive outcome following cardiac surgery on-pump and off-pump [19]. There was no clinical significance when comparing cognitive decline in both groups after five years following cardiac surgery. [19] Danny Chum et al looked at records of 63 047 patient who had had coronary artery bypass grafting (CABG) ,48 648 on pump and 14 389 off pump. Postoperative mortality and strokes were not any lower in the off-pump CABG than in the on-pump CABG. In addition, off-pump CABG was associated high hospital costs and prolonged hospital stay. [20] Diegeler et al also conducted a randomised trial in patients 75 and older for CABG on and off cardiopulmonary bypass (CPB) looking at death, stroke, myocardial infarction, repeat revascularization and renal replacement therapy at 30 days and 12 months.[21] The results showed no significant difference in outcome between the two groups at both at 30 days and 12 months.[21] This means there was no significant difference in either of the operative approaches as the above mentioned clinical outcomes did not change at thirty days and one year in either group .

In our study cerebral oximetry monitoring was a technique utilised by study participants in monitoring and adequately managing cerebral blood flow. Near InfraRed Spectroscopy (NIRS) can be used to monitor regional cerebral oxygen saturation which would be a reflection of cerebral oxygen supply and demand. [22]One study hypothesized that the real time autoregulation monitoring using the NIRS based method was more accurate in determining the lower limits of autoregulation during CPB than the empiric determination based on age, preoperative history, and preoperative blood pressure.[7] Results showed a wide range of MAPs at the lower limits of autoregulation in patients on CPB making estimating this target difficult. Real

time monitoring of autoregulation with cerebral oximetry monitoring may provide more rational means of individualizing MAP during CPB. [7] The question remains whether the use of cerebral saturation monitoring improved neurological outcomes in patient undergoing cardiac surgery. A systemic review by Zheng at el [23] assessed whether a decrease in cerebral saturation during cardiac surgery was associated with stroke, postoperative cognitive dysfunction (POCD), delirium and whether correction of the low cerebral saturation improved neurological outcomes. [23] It found that the evidence supporting postoperative neurological complications was due to low cerebral saturations was low and that its correction did not improve outcome. Moreover things such as malposition of the cannula during CPB can cause a decrease in cerebral saturation.[23]

In this study there was a difference in practice amongst registrars and anaesthesiologist with the use of corticosteroids, dexmedetomidine and opioids as pharmacological agents for neuroprotection during cardiac surgery. There was similarity with understanding of use magnesium sulphate, volatile and intravenous anaesthetic in use for neuroprotection. The concept of neuroprotection is receptor mediated protective action, which refers to protecting the brain from further damage after the initial insult. [8] The pharmacological protective benefits are short-term as studies have failed to demonstrate long term protection by anaesthetic agents. [8]

Cardiopulmonary bypass offsets an inflammatory response. Steroids are good anti-inflammatory agents, they suppress the inflammatory response, which is associated with morbidity and mortality in cardiac surgery. [24] The effectiveness of steroids in neuroprotection was investigated in the SIRS randomised doubled blinded clinical trial, patient received methylprednisolone 250mg at induction and initiation of bypass and others placebo. [24] The primary outcome was mortality, composite of death, and major

morbidity (MI, stroke, renal and respiratory failure) within 30 days. Methylprednisolone compared to placebo did not reduce the risk of death and major morbidity including stroke at 30 days. This study did not support routine administration of steroids in patient undergoing cardiopulmonary bypass. [24]

Lignocaine is also said to have anti-inflammatory properties as it reduces cerebral inflammation. [25] Matthew et al assessed the potential of intravenously administered lignocaine to reduce postoperative cognitive dysfunction after cardiac surgery on cardiopulmonary bypass. [25] Lignocaine was administered as a bolus at 1mg/kg followed by a continuous infusion for 48 hours in the control group. Its administration did not reduce post operative cognitive decline and in diabetic patients it increased their susceptibility to post operative cognitive dysfunction. [25] In another randomised double blinded control trial lignocaine was administered for twelve hours as an infusion in the control group. [26] Cognitive testing, self-rating memory tests were administered before surgery, and at ten and 25 weeks postoperatively. The results showed that lignocaine was not neuroprotective as there was no difference between the two groups. [26]

Dexmedetomidine is shown to be neuroprotective, this was demonstrated in a double blinded randomized control trial conducted in 106 mechanically ventilated patients by measuring delirium, coma and a percentage of days spent within 1 point of the RASS (Richmond Agitation Sedation Scale).[27] They were sedated with either dexmedetomidine or lorazepam. The patient group sedated with dexmedetomidine had more days without delirium or coma and spend more time within 1 RASS point of their sedation goal in compared to the lorazepam group. [27] A study by Su X et al also

demonstrated that dexmedetomidine decreased post operative delirium in patients undergoing none-cardiac surgery. [28] The patients received dexmedetomidine or placebo administered at 0,1mcg/kg/hour with decreased incidence of delirium in the dexmedetomidine group . [28]Dexmedetomidine, with its anti-inflammatory properties, inhibits inflammation in ischaemic brain tissue by alpha 2 adrenergic receptor activation.[29] At present there is a randomised controlled trial that is assessing cognitive outcome after dexmedetomidine sedation in cardiac surgery in older patients. [30] It is hoped that the results will shed some light on neuroprotective effects of dexmedetomidine.

The neuroprotective effects of magnesium sulphate during cardiac surgery is attributed in its ability to stabilise the electrochemical membrane, reduce excitotoxicity and intracellular calcium release. [31] One randomised control trial demonstrated the neuroprotective effects of magnesium sulphate to be short term. At three months there was improved postoperative neurological function, specifically improved short-term memory and cortical control over brainstem function after cardiac surgery in the control group which had received magnesium intraoperatively. [31] Another randomized controlled trial failed to demonstrate the neuroprotective benefit of magnesium sulphate. [32] A systemic review by Chen et al compared the neuroprotective effects of inhalation anaesthetic agents versus total intravenous agents (TIVA), and 13 studies were selected for review. Data suggested that volatile agents provided better neuroprotection than TIVA in patient undergoing cardiac surgery. [33] In a study on rats, Zhang at el found that the activation of delta opioid receptors protected against glutamine induced cortical neuronal injury. [34] Glutamate mediates injury to neurons

during hypoxic periods. [34] Activation or inhibition of the delta opioid receptors alters the susceptibility of neurons to hypoxia. [34] Further research is needed in humans.

Most of the finding in our study were similar to those of a study conducted by Krause et el, [3] although efforts to standardize care to reduce stroke and cerebral injury post cardiac surgery were promising, they were still low and like our setting. The availability of institutional statistics on the rates of stroke or cerebral injury was much better compared to our study. When assessing atheromatous burden TEE was the favoured method in both studies despite epi-aortic scanning being superior. With the lack of guidelines for blood pressure management during cardiac surgery, participants reported aiming for a MAP of above 65 mmHg in both studies. They reported their CABG cases being performed on pump and the practice of double aortic clamping was low which is in keeping with the results of our study. Cerebral oximetry monitoring was reported to be used mostly in high-risk cases while in our setting it was utilised in almost all the cardiac cases.

Limitations

Almost all the participants are based in the public sector meaning the results reflects practice in this sector which leaves a knowledge gap about the private sector. This study gave insight into current practice especially in the public sector. Despite all the limitations, this study was the first of its kind in our setting.

Conclusion

The results of this study demonstrate that there is a lack of guidelines resulting in variability in practice clinical amongst clinicians. On the other hand, the literature from most studies is equivocal about the applied methods that are thought to be neuroprotective during cardiac

surgery. The poor reporting of the incidence of strokes and cerebral injury at most institutions should be concerning. More work is needed in setting up guidelines for practice during cardiac surgery to standardize care and improvement in adverse outcome reporting and collection of this data. Once care is standardized it would be easier to assess if implemented practice improved outcomes

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APPENDIX 1: Proposal

Neuroprotective strategies in cardiac surgery

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1. Introduction

Neurological complications or adverse neurological outcomes post cardiac surgery result in increased morbidity and mortality. The incidence of strokes following cardiac surgery is reported to be 2 to 4%, and it's much higher in a patient with a previous history of a stroke, [1] while postoperative cognitive dysfunction (POCD) is as high as 53% at hospital discharge. [2] The adverse neurological outcome post cardiac surgery have been well described and are an important cause of significant complications. [1] Adverse neurological outcomes have been classified by the American College of Cardiology (ACC) and American Heart Association (AHA) into type 1 and 2 neurological deficits. [3]

Type 1deficits are associated with major focal neurological deficits, stupor or coma; and type 2 deficits are defined by the deterioration in intellectual function. [3] Predictors for type 1 neurological deficit include aortic atherosclerosis, prior history of neurological disease, use of intra-aortic balloon pump (IABP), diabetes mellitus (DM), hypertension, unstable angina and advanced age. [3] Predictors for type 2 neurological deficit include excessive alcohol intake, dysrhythmias such as atrial fibrillation, hypertension, a history of previous cardiopulmonary bypass surgery (CPB), peripheral vascular diseases (PVD) and congestive cardiac failure. [3]

The aetiology of POCD is poorly understood and is thought to be multifactorial; which includes surgical, anaesthetic and patient factors. [1] In a retrospective study involving 1408 CPB procedures, an analysis of perfusion parameters was conducted; 4 clusters of patients were formed based on the similarity in their parameters. [4] The parameters

measured were mean arterial pressure (MAP) and its dispersion, dispersion of systemic vascular resistance (SVR), dispersion of arterial pulse pressure, and the maximum value of mixed venous saturation ($ScvO_2$). Patients who underwent CPB procedures with large fluctuation in haemodynamic parameters had an increased risk of developing postoperative neurological complications. [4]

Cerebral autoregulation occurs if cerebral perfusion pressure (CPP) is within a normal physiological range. The target optimal arterial pressure during CPB has not yet been defined. [1] During CPB the mean arterial pressure (MAP) is usually maintained at 60mm Hg. [1] This number is arbitrary, and it is dependent on the patients age, preoperative blood pressures and their medical history. [1]

A retrospective study involving 1000 patients who went for coronary artery graft looked at the influence of CPP and MAP dispersion on neurological outcomes. [4] Their results showed that it was not only age, duration on CPB and a history of previous strokes that contributed as risk factors, but that a high MAP fluctuation had the highest incidence of stroke development in these patients. [4]

The measurement of decreased cerebral saturation is one area of interest that can possibly help in monitoring for the possibility of POCD post cardiac surgery. [5] Devices such cerebral oximetry may be used to maintain cerebral oxygen saturation within a certain range, based on measurements taken preinduction of anaesthesia. Near infrared spectrometry (NIRS) can be used clinically to monitor cerebral blood flow. [6] One study hypothesized that the real time autoregulation monitoring using the NIRS based method was more accurate in determining the lower limits of autoregulation

during CPB than the empiric determination based on age, preoperative history, and preoperative blood pressure. [6] Results showed a wide range of MAPs at the lower limits of autoregulation in patients on CPB making estimating this target difficult. Real time monitoring of autoregulation with cerebral oximetry monitoring may provide more rational means of individualizing MAP during CPB. [6]

Cerebral microembolisation during CPB may lead to cognitive decline after cardiac surgery. [7] Embolic materials can be derived from the CBP circuit and from aortic lesions. Aortic atherosclerosis in itself may be a source of emboli especially during aortic cannulation or cross clamping. [1] Transfusion of the patients own unprocessed blood into CPB circuit is common practice to reduce blood loss and rate of transfusion. [7] Processing of collected blood with a cell saver before transfusion may reduce cerebral microembolization and reduce POCD. [7] This was demonstrated in a study whereby 226 patients were randomised into a group receiving cell saver processed blood and the other unprocessed blood. The study demonstrated that the processing of shed blood prior to transfusion results in clinically significant reduction in cognitive dysfunction postoperatively. [7] This further emphasizes the clinical importance of lipid embolization in contributing to postoperative cognitive decline in patients exposed to CPB. [7]

Anaesthetic and surgical factors are hard to delineate from each other as a cause of POCD. Conflicting evidence exists as to whether intravenous or volatile anaesthetic agents are implicated in the development of POCD. [1]

Aida et al., classifies neuroprotective strategies during cardiac surgery with CPB into surgical and pharmacological brain protection methods. [8] Lowering core body temperature via CPB and additional surface cooling has been shown to prevent injury to the brain and spinal cord, however, controversies exist with regards to the extent of cooling between higher hypothermic (20 -28˚C) and deep hypothermic (10 -13˚C) cooling. The benefits of lower temperatures include decreased metabolic activity and longer predicted safety interval for surgery, however, complications do exist such as the risk of bleeding. [9]An animal study looked at the influence of different flow rate and temperature on MAP, jugular and regional flow saturation, and histological markers of brain damage. [10] This study demonstrated that reduced MAP during hypoperfusion leads to reduced carotid artery blood flow, reduced tissue oxygen saturation, increased lactate and malondialdehyde levels and histological damage to the hippocampus. Brain damage was less in the hypothermic group compared to the normothermic group. [10]

The CPB circuit initiates an inflammatory response through the activation of leucocytes, platelets, endothelial cells, the coagulation system as well as the fibrinolysis. These potentially have adverse influences on the patient's outcome can be minimized by using leucocyte filters, heparin coated tubing or tubes coated with certain polymers. [11]

There exists a debate on the advantages of off-pump versus on-pump coronary artery bypass graft (CABG). [12] The Octopus study in 2007 investigated the longterm cognitive outcome following cardiac surgery on-pump and off-pump respectively. [12] There was

no clinical significance when comparing cognitive decline in both groups after five years following cardiac surgery. [12]

The duration of CPB during cardiac surgery has been associated with a variety of adverse outcomes. [12] Longer durations on CPB are a risk factor for neurological injury post cardiac surgery, [14] however in a meta-analysis by Habibi et al, the use of lignocaine infusion in combination with long CPB times was associated with more favourable neurological outcomes. [14]

Clinical studies and literature advise against high MAP during cardiac surgery. [12] The current anaesthetic practice supports low MAP in decreasing POCD following cardiac surgery, but the evidence- based threshold has not been determined. [13] Low MAPs are associated with decreased bleeding and thromboembolic phenomena. [15] In a meta-analysis by Kiabi et al. neuroprotective effects of low MAP during cardiac surgery were investigated, and the maintenance of MAP below 80mmHg did not show a decline in the rate of POCD in post cardiac surgery on CPB. [16]

Selective brain perfusions techniques such as antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP) are utilised during induced hypothermia, and several studies have compared the mode of brain perfusion and temperature management. [17] Clinical evidence favours the use of ACP.[17] Leshnower et al. conducted a study comparing deep hypothermic cardiac arrest (DHCA) with RCP; and mild hypothermic cardiac arrest (MHCA) with ACP; there was no difference in neurological fallout as only one patient in each group sustained a cerebral-vascular accident. [18]

Hyperglycaemia is defined as serum glucose levels of more than 7.8 to 11 mmol/L (140-180 mg/d/L) in hospitalised patients. [19] Elevated plasma glucose levels in cardiac

surgery are stress response mediated, induced by surgical, anaesthetic and CPB factors.[20-21] The mechanism causing neurological effects involves an increased lactate production substrate, more release of glutamate and aspartate and general enhancement of the inflammatory process. [22] Hyperglycaemic control is therefore important in the perioperative period. [12]

The use of processed electroencephalogram (EEG) or bispectral index (BIS) monitoring, NIRS, transcranial doppler ultrasound, alongside other physiological monitors should be used routinely to detect and prevent damage resulting from ischaemic hypoxia, embolism, hypocapnia, arterial hypotension, low cardiac output, and variation in temperature during cardiac surgery and in the postoperative period. [12] More data is showing that these technologies can assist in identify adverse events and may predict adverse outcomes. [23]

The modern concept of neuroprotective strategies during cardiac surgery is specific, receptor-mediated protective action, i.e., protecting the brain from evolving damage after initial insult. [12] However, despite impressive short-term protection, most experimental studies have failed to show long term protection by anaesthetic agents. There current anaesthetic neuroprotection approaches, aim at reducing the severity of the insult as opposed to complete neuroprotection. [12]

The focus of neuroprotection has moved from just reduction of energy consumption to receptor mediated protection, barbiturates block glutamate receptors, potentiate GABA-ergic activity and inhibit calcium influx, but they

are associated with systemic immunosuppression, increased risk of infection, prolonged effects, and reduced cerebral blood flow (CBF) as a result they are less popular as a drug of choice for neuroprotection. [24] The proposed neuroprotection

strategies with the use of propofol include sodium channel blockage via excitotoxin mediation, antioxidant properties, and anti-inflammatory or anti-apoptotic mechanisms. [25]

Volatile anaesthetic agents may provide neuroprotection through reduced excitotoxicity, improved calcium regulation, increased CBF, downregulation of metabolism, reduction of oxidative stress, and increased potassium channel activity. [26] No consensus has been reached on which volatile is best and the appropriate dose to provide neuroprotection.

A meta-analysis compared the neuroprotective effects of total intravenous anaesthesia (TIVA), versus volatile anaesthesia in patients undergoing CPB. Mini-mental state examination scores were significantly higher in the volatile agent group compared to the propofol, ketamine and thiopentone infusions. [27] Experimental data suggests that volatile agents are neuroprotective by their preconditioning and postconditioning mechanisms, the increased tolerance of neurones against subsequent lethal insults and the reduction of inflammatory markers. They have been shown to improve postoperative neurocognitive function and CBF. [28]

The neuroprotective effects of lignocaine lie in its ability to cross the blood brain barrier, blocking sodium ion channels, and reducing cerebral inflammation. [29] Lignocaine has also however been shown to predispose diabetic patients to POCD. [30] Higher lignocaine concentrations are associated with more substantial neuroprotective effects; this was demonstrated in a meta-analysis involving 688 patients, where lignocaine was administered as an infusion from anaesthetic induction until 48 hours postoperatively. [31] At higher infusion rates of 1-2mg/kg/h or 1-2mg/min, lignocaine increased susceptibility to complications such as myocardial ischaemia and

reperfusion injury. [32] Although the evidence is conflicting, lignocaine has a role as a neuroprotective agent, but further studies are needed. [12]

Ketamine and Xenon (Xe) are both N-Methyl D-Aspartate (NMDA) receptor antagonists. Ketamine is a neurotransmission inhibitor and an anti-inflammatory agent. It increases regional CBF in a concentration dependent manner in all brain regions with limited incidence of POCD and postoperative delirium. In major surgery, ketamine is associated with increased hallucination and nightmares postoperatively. [33] However, uncertainty still exists regarding its role as a neuroprotective agent. [12] Inhaled Xe (70%) during 60 min of focal cerebral

ischaemia in mice improved neurological function and reduced infarct size at 24 hours of reperfusion compared to 70% nitrous oxide. [24] While Xe does demonstrate neuroprotective effects in animal studies, clinical evidence is insufficient on its potential as a neuroprotective agent in cardiac surgery. [12]

Dexmedetomidine improves neurological dysfunction in mechanically ventilated patients and in elderly patients in the intensive care unit post noncardiac surgery and has been shown to decrease mortality in critically ill septic patient. [34] It attenuates central sympathetic activity, inhibits inflammation in ischaemic brain tissues via alpha $_2$ adrenergic receptor activation [34], it protects against neuro apoptosis and has drug sparing effects through its opioid/GABA-nergic receptor activity. [35] In animal studies, dexmedetomidine has demonstrated to be superior to propofol, etomidate and volatile agents in reducing anaesthetic and surgical induced learning and memory deficits. [35]

Magnesium sulphate has vasodilatory effects, stabilises the electrochemical gradients, inhibits glutamate at the NMDA receptors, and has an ability to reduce intracellular calcium release. [36] Magnesium has demonstrated to be effective in

improving short term outcomes of postoperative memory and cortical control over brainstem function after cardiac surgery.[37] Low dose magnesium sulphate, like lignocaine is a promising neuroprotective agent, but clinical evidence on its effectiveness in preventing stokes and ischaemic events, as well as prevention of POCD is required. [12]

An osmotic agent such as mannitol is a possible option in the prevention or treatment of POCD. Cerebral oedema is an independent risk factor for postoperative neurocognitive decline. Evidence for the use of mannitol is however very limited in support of this, with few large, randomised control trials. [38] Vasodilating agents such as nitric oxide and chlorpromazine have also been suggested but supporting clinical evidence is very limited.[39]

Despite this high incidence of neurological complications associated with cardiac surgery on CPB, there are still no established standardised clinical guidelines for neuroprotection monitoring and prevention in the perioperative period.[40] A survey done by Krause and colleagues concluded that this lack of guidelines has a huge impact on patients' neurological outcomes.[40] They advocated for more studies to be conducted in helping to change our practice.

2. Problem statement

The occurrence of neurological injury and cognitive disorders post cardiac surgery is well known and described in literature. Neuroprotective strategies intraoperatively can significantly improve postoperative neurological outcome. The current challenge is the lack of standardised practice or protocol for intraoperative neuroprotection during cardiac surgery.

3. Aim

The aim of this study is to ascertain current neuroprotective strategies employed by South African anaesthetists during cardiac surgery, by assessing their use of commonly employed strategies.

4. Objectives

The objectives of the study are:

- To determine current neuroprotective strategies applied in cardiac surgery: such as assessment of aortic burden plague, management of intraoperative blood pressure, use of cerebral oximetry and pharmacological methods.
- To compare the practices amongst the clinicians

5. Research assumptions

The following definitions will be applied in this study:

Neurological complication: refers to cerebrovascular accidents (CVAs) and postoperative cognitive dysfunction (POCD)

Neuroprotection: preservation of neuronal structure or function

Atheromatous burden: the summed volume of the atheromatous plague

Cardiac surgery: surgery of the heart or the great vessels on cardiopulmonary bypass (CPB)

Cardiac anaesthetist: an anaesthetist that provides anaesthesia to cardiac patients regularly (at least 1 to 2 cases per week), either in state or private sector

Registrar: an anaesthetist in training to become a specialist anaesthetist that is or has rotated in the cardiothoracic rotation at an academic hospital

6. Demarcation of the study field

An electronic survey will be distributed among cardiac anaesthetists and registrars involved in giving anaesthesia to cardiac patients coming in for cardiac surgery on CPB. A google link of the survey will be created. To adhere to the protection of personal information act (POPIA), the central administration of the Cardiothoracic Anaesthesia Society of South Africa (CASSA) will distribute the link to the members during the Joint Perioperative Cardiothoracic (JPC) congress on the 20th of November 2021. The central administration of the Society of Anaesthesia of South Africa (SASA) will also be responsible in distributing the link to the survey on their weekly newsletter.

Anaesthetic registrars who have completed or are currently going through their cardiothoracic rotation across the country in the various universities, as well as consults who do at least one case per week. will be eligible to take part in the study.

7. Ethical considerations

Permission to conduct the study was granted by the president of CASSA, the Chief Executive Officer (CEO) of CMJAH, the Head of Department of Anaesthesia at CMJAH and SASA. Ethics clearance has been granted by the Wits Human Research Ethics Committee (HREC) (Protocol Number: M211068). Application to the National Health Research Database (NHRD) has been submitted and is pending approval. Only the researcher will have access to the collected data, which will be kept on a password protected computer and all the responses will be anonymous as no person identifying data will be collected. Consent will be implied by completion of the survey. All collected data will be kept for six years after completion of the study as per HREC guidelines.

8. Research Methodology

8.1 Study design

This is a cross sectional, descriptive, contextual study of cardiothoracic anaesthetist in South Africa.

8.2 Study population

The study will be conducted amongst members of CASSA, other cardiac anaesthesia consultants and anaesthetic registrars across the various universities having completed or currently rotating in the cardiothoracic anaesthetic rotation.

8.3 Study sample

8.3.1 Sample method

In this study, a nonprobability also known as a convenience sampling method will be used. This method uses all easily available participants to be part of the study. The survey will be sent out to all members of CASSA, cardiac anaesthesia consultants and cardiothoracic registrars at various universities.

8.3.2 Sample size

The sample size was calculated in consultation with a statistician considering registered CASSA members and SASA members. The minimum sample size is 140, with a 95% level of confidence. The study population is 220 with a 5% margin of error.

8.4 Inclusion criteria

- All anaesthesiologists who provide anaesthesia services for cardiac surgery on CPB across South Africa, who are registered as members of CASSA and SASA
- Anaesthesia registrars who are/have rotated in cardiothoracic rotation at academic hospitals/ institutions in South Africa

- Consultant anaesthetists from various universities or academic hospitals who provide anaesthesia care to patients requiring cardiac surgery

8.5 Exclusion criteria

- Anaesthetists who do not provide anaesthesia to patients requiring cardiac surgery on CPB

8.6 Data collection

Permission will be sought to utilize a questionnaire by Krause and colleagues, that was designed for a similar study conducted in their setting. This questionnaire has been modified to our setting with the assistance of four senior cardiothoracic consultants in the department of anaesthesia at CMJAH and CHBAH. The survey will be in the form of an electronic survey that will be made accessible to all members of CASSA, the anaesthetic registrars rotating in cardiac anaesthesia and consultants at the various universities or academic hospitals. The link to the electronic questionnaire will be made available to the CASSA and SASA members by the society's central administration team and will also be published on the SASA news later. Each member will receive a link that is unique to them to prevent duplication of responses. There will be an information sheet to explain the purpose of the study. Completion of the survey will be assumed as consent to participate in the study.

8.7 Data analysis

The data is categorical, frequencies and percentages will be utilised to compare the practice amongst clinicians, and the chi square tests for association. If the expected values in cells are less than five, then comparison will be based on the fishers exact

test. Our analysis is based on the 95% confidence level, hence a P value =< 0,05 will indicate significant statistical differences in practice.

9. Significance of the study

Currently there are no established standardised guidelines for neuroprotection during cardiac surgery. This is in the background of high incidences of neurological complications post cardiac surgery and the associated morbidities and mortalities. A survey conducted by Krause and colleagues concluded that the lack of neuroprotective guidelines during cardiac surgery on CPB has a huge impact on patient outcomes postoperatively. This study will be a building block towards developing guidelines for neuroprotection in cardiac surgery and the improvement of patient neurological outcome postoperatively.

10. Validity and Reliability

Validity of a study is defined by how accurately a method measures what it's meant to measure. The questionnaire that will be utilised has a high validity as it was already utilised in a study. The same study will be duplicated and adapted to our setting. The questionnaire was sent to group of 46 experts in the field of perioperative neuroprotection that was suggested by members of Society of Cardiovascular Anaesthesiologists. The experts were asked to assess if the instrument items or questions were appropriate to the targeted assessment of current neuroprotective approaches utilised. Participation in the study will be voluntary and no incentive will be given.

11. Limitations

- The greatest limitation in this will getting the participants to complete the questionnaire.
- Availability of neuroprotective equipment at different institutions; resources in state compared to the private sector.

12. Timeline

	August - September 2021	**September-October 2021**	**November 2021 -February 2022**	**July 2022-September 2022**	**October2022-February2023**
Literature review					
Preparation of protocol					
Ethics application and protocol submission					
Data collection					
Data analysis					
Write up					

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APPENDIX 2: Human Research Ethics Committee clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Nthabiseng Jacqueline Kumalo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M211068

NAME: (**Principal Investigator**)	Dr Nthabiseng Jacqueline Kumalo
DEPARTMENT:	Anaesthesia Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Neuroprotective strategies in cardiac surgery
DATE CONSIDERED:	29/10/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr G. Leballo, Dr P. Motshabi and Dr P. Mogane
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/11/2021

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

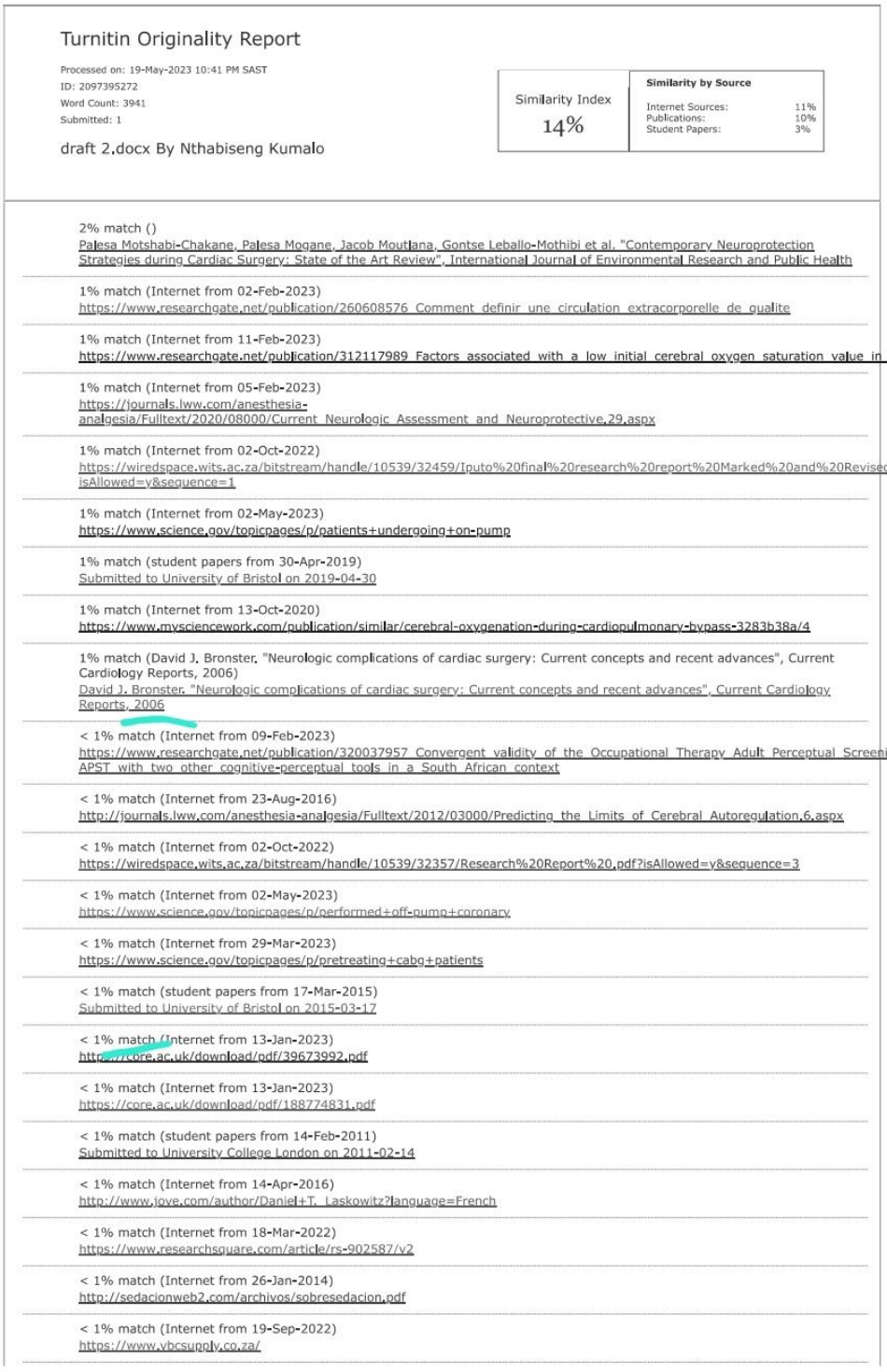
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

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APPENDIX 3: Turn it report cover page



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APPENDIX 4 Journal guidelines to authors

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otherwise they will be lost during conversion to PDF

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When preparing tables, please follow the formatting instructions below.

Tables should be numbered and cited in the text in sequence using Arabic numerals

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Tables less than one A4 or Letter page in length can be placed in the appropriate

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) or comma separated values (.csv). Please use the standard file extensions.

 Table titles (max 15 words) should be included above the table, and legends (max 300

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 Tables should not be embedded as figures or spreadsheet files, but should be

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 Colour and shading may not be used. Parts of the table can be highlighted using

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Research articles and non-research articles (e.g. Opinion, Review, and Commentary articles)

must cite appropriate and relevant literature in support of the claims made. Excessive self-

citation, coordinated efforts among several authors to collectively self-cite, gratuitous and

unnecessary citation of articles published in the journal to which the paper has been

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Citation manipulation will result in the article being rejected, and may be reported to authors'

institutions. Similarly, any attempts by peer-reviewers or editors to encourage such practices

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Authors should consider the following guidelines when preparing their manuscript:

Any statement in the manuscript that relies on external sources of information (i.e. not the

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Authors should avoid citing derivations of original work. For example, they should cite the

original work rather than a review article that cites an original work.

Authors should ensure that their citations are accurate (i.e. they should ensure the citation

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Authors should not cite sources that they have not read.

Authors should not preferentially cite their own or their friends', peers', or institution's

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Authors should avoid citing work solely from one country.

Authors should not use an excessive number of citations to support one point.

Ideally, authors should cite sources that have undergone peer review where possible.

Authors should not cite advertisements or advertorial material.

What should be cited?

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited.

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Authors may wish to make use of reference management software to ensure that reference

lists are correctly formatted.

APPENDIX 5: Charlotte Maxeke Johannesburg Academic Hospital CEO Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms. TT Mahlangu*
Email: Thandi.Mahlangu4@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 28 March 2022

GP_202111_063

Dear Dr. N. Kumalo

RE: FINAL APPROVAL OF STUDY

TITLE: NEUROPROTECTIVE STRATEGIES IN CARDIAC SURGERY

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~
Signed by:Jayshina Punwasi
Signed at:2022-03-30 12:13:03 +02:00
Reason:Witnessing Jayshina Punwasi

Dr J. Punwasi
Senior Clinical Manager

Approved/~~Not Approved~~
Signed by:Gladys Magugudi Bogoshi
Signed at:2022-03-30 16:53:18 +02:00
Reason:Witnessing Gladys Magugudi Bo

Ms. G Bogoshi
Chief Executive Officer

APPENDIX 6: Permission letter by Charlotte Maxeke Johannesburg Academic hospital HOD anaesthesia

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF ANAESTHESIA
Area 361
Charlotte Maxeke Johannesburg Academic Hospital
University of the Witwatersrand
Tel: 011 488 4344
Fax: 086 765 3477

16 November 2021

Dr Nthabiseng Kumalo
Registrar: Anaesthesia
CMJAH

Dear Dr Kumalo

MMED RESEARCH PROJECT

Your proposed research project at CMJAH, titled "Neuroprotective Strategies in Cardiac Surgery", will assist in improving the quality of cardiac anaesthesia service delivery at our hospital.

However, preconditions are that the study has no cost implications to the hospital, does not interfere with service delivery, and must be approved by the relevant research and ethics committees, both at university and hospital levels before data collection starts.

I fully support you in this research endeavor. Looking forward to your findings.

Yours sincerely,

Prof EE Oosthuizen
Clinical head: Department of Anaesthesia
CMJAH

Appendix 7: Permission letter by CASSA president



2023 ICCVA-CASSA CONGRESS

TOWARDS SAFE CARDIOVASCULAR AND THORACIC SURGERY OUTCOMES

DATE: 30 November - 2 December 2023
VENUE: Cape Town International Convention Centre, South Africa

29 May 2022

To Whom It May Concern

This letter serves to confirm that Dr Nthabiseng Kumalo has been granted permission to collect data for research purposes during a CASSA JPC 2022 annual congress.

Yours sincerely

Professor Palesa Motshabi Chakane
Congress Chair

For more information please contact Velocity Vision
Tel: +27 11 894 1278
Web: www.velocityvision.co.za

VELOCITY VISION

Appendix 8: Permission letter by SASSA CEO

SOUTH AFRICAN SOCIETY OF ANAESTHESIOLOGISTS
Official Group Of SAMA
Association Not For Gain
T: +27 (0) 86 010 3137 (share call) T: +27 (0) 31 368 2530 F +27 (0) 86 242 9804
E: sasa@sasaweb.com
PO Box 22511, Glenashley, 4022, South Africa
www.sasaweb.com
VAT Registration Number: 4680223379

19 November 2021

To Whom it May Concern

Dear Sir/Madam

Re: Letter of Confirmation of Support

The South African Society of Anaesthesiologists (SASA) is pleased to be providing a letter of confirmation and support for the M Med Research project about to be undertaken by Dr. Nthabiseng Kumalo. We believe that this particular research will add value to the profession as a whole.

SASA, specifically, confirms that we shall provide Dr. Kumalo with any with statistical information pertinent to her research. We shall, further, provide a platform through which her research survey may be distributed to the SASA membership as a whole. SASA represents over 2 400 members, with over 90% of specialists belonging to the Society.

Should you have any queries in this matter, please do not hesitate to contact me further.

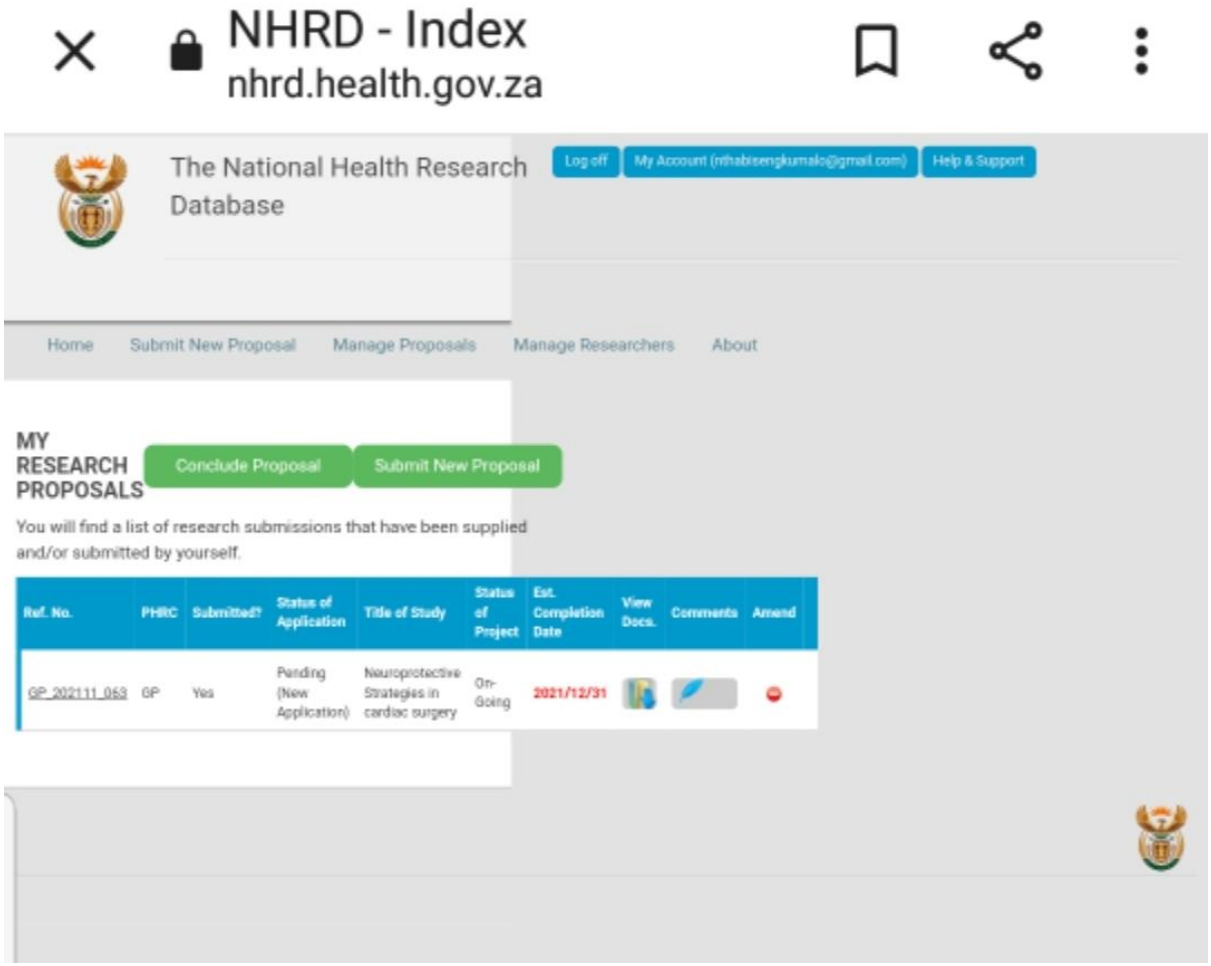
Sincerely,

NZimmelman

Ms. Natalie Zimmelman
SASA CEO

President | Prof. B Biccard **Vice President** | Dr. L Lasersohn
President (Past) | Dr. DHS van Zijl **Chief Executive Officer** | Ms. N Zimmelman
National Secretary | Prof PJHL Fourie **National Treasurer** | Dr. S Chetty

Appendix 9: National Health Research Database application



Appendix 10: Data collection sheet

Questionnaire

1. I work (mark all that apply)

a) ☐ At an academic institution

b) ☐ In private practice

c) ☐ Other

2. I practice in the following province (mark all that apply)

a) ☐ Gauteng

b) ☐ KZN

c) ☐ WC

d) ☐ EC

e) ☐ NC

f) ☐ Limpopo

g) ☐ Mpumalanga

h) ☐ NW

i) ☐Free state

3. My role is (mark all that apply)

   a) ☐ Anaesthesiologist

   b) ☐ Registrar that has completed cardiothoracic anaesthesia rotation

   c) ☐ Other

4. In my practice, I have performed the following approximate number of open-heart procedures

   a) ☐ Less than 200

   b) ☐ 201- 500

   c) ☐ 501-1000

   d) ☐ More than 1000

   e) ☐ I don’t know

5. The rate of strokes/cerebral injury post cardiac surgery is made available to me:

   a) ☐ Yes

   b) ☐ No

6. In my institution there have been organised efforts to standardise care to reduce the incidence of postoperative cardiac surgical stroke and cerebral injury:

a) ☐ Yes

b) ☐ No

c) ☐ I don't know

Please answer questions in the 7 to10 pertaining to the assessment of aortic atheroma during cardiac surgery

7. In my practice, transoesophageal echocardiography (TEE) is performed to assess the aortic atheromatous burden (choose all that apply):

   a) ☐ In all cardiac surgery patients requiring aortic cannulation

   b) ☐ Never

   c) ☐ In patients at increased risk of peri-operative embolic events

   d) ☐ At the surgeon's request

   e) ☐ At the anaesthesiologist's request

   f) ☐ According to standardized institutional guidelines/standard operating procedure

   g) ☐ I don't know

8. In my practice, epi-aortic scanning is performed (choose all that apply):

   a) ☐ In all cardiac surgical patients requiring aortic cannulation

   b) ☐ Never

c) ☐ In patients at increased risks of perioperative embolic events

d) ☐ At the surgeon's request

e) ☐ At the anaesthesiologist's request

f) ☐ According to the standardised institutional guidelines/standard operating procedure

g) ☐ I don't know

9. In my practise, double clamping of the aorta during coronary artery bypass grafting (CABG) is performed in approximately the following percentage of all CABG cases:

a) ☐ 81%-100%

b) ☐ 61%-80%

c) ☐ 41%-60%

d) ☐ 21%-40%

e) ☐ 0%-20%

f) ☐ I don't know

10. In my practice, off-pump CABG is performed in approximately the following percentages of all CABG cases:

a) ☐ 80%-100%

b) ☐ 61%-80%

c) ☐ 41%-60%

d) ☐ 21%-40%

e) ☐ 0%-20%

f) ☐ I don't know

Please answer questions 11 and 12 pertaining to clinical management of arterial blood pressure during cardiac surgery

11. My institution has standardised guidelines/standard operating procedures in place for managing blood pressures in cardiac surgery patients during the following (choose all that apply):

    a) ☐ Intraoperatively, excluding Cardiopulmonary bypass

    b) ☐ During Cardiopulmonary bypass only

    c) ☐ Only in high-risk patients

    d) ☐ There are no standardised intuitional guidelines/standard operation procedures in place

    e) ☐ I don't know

12. In my institution, we routinely target the following a mean arterial blood pressure (MAP) during CPB for patients thought to be at risk for postoperative cerebral injury:

    a) ☐ >45mmHg

    b) ☐ >55mmHg

c) ☐ >65mmHg

d) ☐ >75mmHg

e) ☐ >85mmHg

f) ☐ We use a goal- directed perfusion algorithm to determine MAP goals

g) ☐ We do not target any specific MAP

h) ☐ Other

i) ☐ I don't know

Please answer question 13 and 14 pertaining to perioperative cerebral monitoring and protection during cardiac surgery

13. In my institution, I use cerebral oxygen saturation monitoring, e.g. near infrared spectroscopy (NIRS) to guide therapy (choose all that apply):

a) ☐ In all cardiac surgical patients

b) ☐ Never

c) ☐ In patients at increased risk of peri-operative cerebral injury

d) ☐ At the surgeons' request

e) ☐ At the anaesthetist's request

f) ☐ According to standardised institutional guidelines/standard operating procedures

g) ☐ I don't know

14. My institution has in place standardised treatment strategies/standard operating procedures in place for cerebral protection during cardiac surgery (choose all that apply):

    a) ☐ For all cardiac surgery patients

    b) ☐ Only for patients at increased risk for cardiac for perioperative cerebral injury

    c) ☐ This is surgeon specific

    d) ☐ There are no standardised treatment strategies in place

    e) ☐ I don't know

15. In my practice, I use one/more of the following pharmacological agents as a protective strategy to reduce possible neurological injury during cardiac surgery:

    a) ☐ Corticosteroids

    b) ☐ Lignocaine

    c) ☐ Dexmedetomidine

    d) ☐ Magnesium sulphate

    e) ☐ Volatile agents

    f) ☐ Intravenous induction agents (e.g. Propofol)

    g) ☐ Opioids

    h) ☐ None

i) ☐ Other (please specify)

If pharmacological agent(s) were selected in Question 15 above, please answer Question 16. If not, please skip to Question 17

16. To your knowledge, is the pharmacological agent(s) chosen above supported by good scientific evidence? Would you advocate for its use, especially when teaching junior anaesthetists?

17. Please write any comments to the study team here: